The Effects of Smoking and Nicotine Replacement Therapy on Blood Pressure

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Over the past 40 years or so, numerous publications have addressed the effects of cigarette smoking on blood pressure. They have provided conflicting information. A series of laboratory experiments clearly demonstrated that smoking a cigarette raises blood pressure, while epidemiologic studies showed that people who smoke tend to have lower rather than higher blood pressure than nonsmokers. This raises the question of whether both of these observations can be true, and also the broader question as to the extent to which laboratory studies of blood pressure on the one hand, and conventional clinic measurement of blood pressure on the other, give us an accurate estimate of the "true" blood pressure. By this we refer to an individual's average level of pressure over a relatively long period of time, which is the pressure that we think is responsible for most, if not all, of the adverse consequences of hypertension. More recently, there have been several studies involving ambulatory monitoring of blood pressure, which might be expected to resolve this issue.

ACUTE EFFECTS OF SMOKING

Studies in which both intra-arterial and indirect blood pressure recording were used have shown that the acute effects of smoking a cigarette include increases in both blood pressure and heart rate, which may last for up to 1 hour.[1] The height of the increase is roughly proportionate to the nicotine content of the cigarette. A classic study was performed by Cryer et al.,[2] who showed modest increases in blood pressure and heart rate after the smoking of a single cigarette; the increases peaked at 15 minutes and were accompanied by increases in plasma norepinephrine and epinephrine. The blood pressure and heart rate changes were blocked by α and β blockade, indicating that they were mediated by the sympathetic nervous system. One might suppose, therefore, that smoking causes increased sympathetic nerve activity, but a study in which this was measured directly from the peroneal nerve[3] showed that despite increases in heart rate, blood pressure, and plasma norepinephrine, muscle sympathetic nerve activity actually decreased after a cigarette was smoked.

What is going on? One explanation is that the increase in blood pressure switches off central sympathetic outflow by activating the baroreflex. Support for this mechanism was provided by a study in which the blood pressure increase was prevented by sodium nitroprusside infusion.[4] In this case, smoking did produce a marked increase in sympathetic nerve activity. In addition, sympathetic activity in the skin, which is not influenced by the baroreflex, increased after smoking, even without nitroprusside infusion. However, if central sympathetic outflow declines while the blood pressure rises, we need another explanation for the increase in blood pressure, such as a more peripheral sympathetic effect triggering norepinephrine release from sympathetic nerve endings. Actually, we have known for more than 100 years that nicotine stimulates sympathetic ganglia, a phenomenon employed by Langley and Dickinson[5] in their classic work on separation of the musculoskeletal and autonomic nervous systems.

EPIDEMIOLOGIC STUDIES

The first observation that smokers have lower clinic blood pressures than nonsmokers was made in an epidemiologic study from Finland, published in

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1959.[6] Since then, a number of other studies have found that blood pressure is either lower or the same in smokers as in nonsmokers, the average difference being about 2–8 mm Hg for systolic pressure and 1–5 mm Hg for diastolic.[1] None of these studies reported that smokers have higher blood pressure. The most obvious explanation for this paradox is that smokers weigh less than nonsmokers (on average, about 1 pound less), but this difference is not enough to account for the blood pressure differences. The largest epidemiologic study, the Health Survey for England,[7] in which 33,860 adults were surveyed, smoking was related to blood pressure, alcohol intake, and obesity. An analysis that controlled for these confounding variables showed that blood pressure was slightly higher in older men who smoked, but otherwise there were no substantial differences between smokers and nonsmokers.

SMOKING AND AMBULATORY BLOOD PRESSURE

Studies comparing ambulatory blood pressure in smokers and nonsmokers have, to some extent, helped to explain this paradox. In 1991, we compared the clinic and 24-hour pressures of 59 hypertensive smokers (all of whom smoked at least one pack per day) and 118 nonsmokers.[8] As expected, we found similar clinic pressures between the two groups, but when we divided the subjects according to age, we found that smokers had significantly higher ambulatory blood pressures during the day (when they were presumably smoking), but not during the night (when they were presumably not smoking). However, this difference was seen only in the older subgroup (aged 55 or more).

A number of other studies have addressed the same question, but with highly varied findings. Elevated daytime and normal nighttime pressures in smokers were confirmed by Purtak et al.,[9] while Hansen et al.[10] found similar daytime pressures but lower nighttime pressures in smokers. Stewart's group[11] found no difference in either daytime or nighttime pressures, and Mikkelsen and colleagues[12] found both pressures to be lower in smokers. Thus, the most consistent finding was a greater day-night difference in blood pressure in smokers. One study[11] that showed no difference in blood pressure levels demonstrated increased daytime blood pressure variability in smokers, although these changes could not be directly related to smoking. After smokers had allegedly refrained from smoking for 1 week, their blood pressure levels were unaffected, although daytime blood pressure variability increased even more. Mikkelsen et al.[12] found that the "white coat" effect (defined as the difference between the clinic and daytime ambulatory pressure) was smaller in the smokers, and suggested that this might explain the apparently higher daytime pressure in smokers, if smokers and nonsmokers were originally matched on clinic pressures.

A more consistent finding is that heart rate is higher in smokers than in nonsmokers throughout the day and night,[11,13,14] and decreases after 1 week of abstinence from smoking.[11] This is consistent with sustained sympathetic arousal in smokers, but not with a heart rate increase in the absence of a blood pressure increase.

CAN THE DIFFERENCES BETWEEN THE ACUTE AND CHRONIC EFFECTS BE EXPLAINED BY TOLERANCE?

Clearly, the acute and chronic cardiovascular effects of smoking are very different. Acutely, there is a pronounced increase of blood pressure and heart rate, which gradually tapers off, but when a second cigarette is smoked, the levels are still elevated and there is a smaller increment in both.[3] This has implications regarding the phenomenon of cardiovascular events peaking in the morning hours. After overnight abstention from cigarettes, the first smoke of the day will produce a much greater cardiovascular surge than subsequent smokes,[15] which plausibly contributes to the rupture of vulnerable plaques. Chronic tolerance to many of the effects of nicotine is well described, and may occur because of down-regulation of nicotine receptors.[16]

ARE NICOTINE PATCHES SAFE IN HYPERTENSIVE SMOKERS?

One component of the Agency for Healthcare Research and Quality (AHRQ) official guidelines for helping smokers to quit is the use of nicotine patches.[17] If nicotine is really the culprit in sympathetic activation, this raises the issue of whether hypertensive smokers who use nicotine patches, which are applied for 24 hours at a time, are subject to further increases in blood pressure. Fortunately, we have an answer, which, while reassuring in terms of the safety of the patches, further clouds the issue of what causes the adverse cardiovascular effects of smoking.

The cardiovascular effects of the patches were examined in two studies. The first[18] was an inpatient investigation of 12 normotensive smokers who received three doses of transdermal nicotine (21, 42, and 63 mg/24 hours) and a placebo patch, each for 5 days, in a balanced order. For the first 4 days of each period, the subjects smoked, and they abstained on the 5th day. Ambulatory blood pressure and heart rate were measured on day 3 (when the subjects were smoking); blood cotinine levels and urine catecholamine

levels were also measured on days 4 and 5. The main conclusion was that none of the nicotine patches had any effect on heart rate or blood pressure, although urine epinephrine was increased. Urine norepinephrine was unaffected. The authors' explanation for the lack of any sustained cardiovascular effect of nicotine was that when it is given in a sustained dose, as with the patch, tolerance to its cardiovascular effects develops within about 35 minutes.

In the second study,[19] the effects of low-dose nicotine patches (21 mg/24 hours) were assessed over a 4-hour period in normotensive nonsmokers (controls), normotensive smokers, and hypertensive smokers. In the controls, there was a progressive increase in heart rate and blood pressure after about 30 minutes, followed by headache and nausea. In the normotensive smokers, blood pressure rose, but there was no change in heart rate. Surprisingly, in the hypertensive smokers neither blood pressure nor heart rate showed any change. This finding thus suggests that it is safe for hypertensive smokers to use nicotine patches, at least at the lowest dose. The explanation for the different effects of nicotine on blood pressure in the three groups may perhaps be explained by tolerance to nicotine. Why there was no effect on blood pressure in the hypertensives is unclear, although they tended to smoke a little more than the normotensive smokers, and perhaps had developed greater tolerance.

CONCLUSIONS

The effects of nicotine are complex. Although smoking acutely raises blood pressure and heart rate, presumably through an effect on the peripheral sympathetic nerves, tolerance develops over time, so that the effects are not sustained. The studies with ambulatory recording, which included periods when people were actually smoking, suggest that any effect is small, may be manifested as a slight increase in daytime over nighttime pressures, and is more pronounced in older than in younger people. Finally, the epidemiologic studies in which blood pressure was recorded when the participants were not smoking have generally shown no significant effect on blood pressure. As a corollary to this, nicotine patches seem to have little adverse effect on the cardiovascular system, and can be safely recommended to patients with hypertension.

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